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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,838	09/05/2003	Jianjun Cheng	ITI-P01-008	8403

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EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,838	CHENG ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *21-26 and 28-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,27,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/28/03, 7/30/04*. 10/18/04, 10/25/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-20, 27, 34 and 35, in the reply filed on February 13, 2006, is acknowledged. The traversal is on the ground that a search of the compounds would necessarily include a search of the methods of use and would present no additional burden. This is not found persuasive because the search of the compounds does not necessarily include any particular method of use unless there is only one unique use. That is clearly not the case in with the instant compounds, as set forth in the original restriction requirement. The examiner respectfully disagrees as to the lack of additional burden. Regarding the election of species requirement, Applicant cogently traverses this requirement, and it is withdrawn.

It is noted that the method of preparing the products was not restricted from the product because of the generic wording of the claim. However, if the method is amended to require more particular action, this may necessitate further restriction.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 recites a dosage form comprising a therapeutically effective amount of a compound of claims 1, 2, 3 or 4. However, the claim does not recite the purpose for which the compound is to be effective. Therefore, the claim is rendered vague and indefinite.

Claim 27 is drawn to a method of preparing a compound of claims 1, 2, 3 or 4. However, the claim recites no particular steps for this method. The claim is rendered vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 5, 7, 10-18, 20, 27, 34 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al (WO 00/01734).

Gonzalez discloses linear biodegradable cyclodextrin (CD) copolymers for the delivery of therapeutic agents. See abstract and reference claims. The reference further discloses a method of preparing said copolymers as well as an embodiment wherein a folic acid moiety is covalently attached to a copolymer. See examples. In the reference, the folic acid moiety is described as a "ligand," similar to the "targeting ligands" in the instant invention. However, the "ligands" in the art and the "therapeutic agents" of the claims are not mutually exclusive groups. For example, in the cited embodiment, folic acid is consistent with Applicant's definition of therapeutic agent.

The reference is silent regarding the status of folic acid as a receptor agonist or antagonist. The burden is on Applicant to demonstrate that folic acid is neither an agonist nor antagonist of some receptor.

The reference is silent regarding the molecular weight of the CD polymer. However, in view of the description of preferred embodiments at pp 11-13, it would appear that the polymer would be encompassed by at least one of the ranges recited in claims 16-18.

Regarding claim 34, the reference is silent regarding the number of folic acid moieties incorporated into the CD polymer. However, the reference specifically suggests the presence of more than one ligand in the polymer. See page 13, lines 19-27. Therefore, it appears more likely than not that the disclosed folic acid conjugate meets the limitations of this claim. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 1- 20, 27 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Kosak (US 6,048,736).

Kosak discloses an aqueous solution comprising a CD polymer covalently attached to gamma globulin via an amide linkage. See Preparation IV at col 22-23. As with folic acid above, the gamma globulin is described as a biorecognition molecule (targeting ligand). However, gamma globulin has known therapeutic activity.

The reference further discloses a CD polymer with "completely entrapped" doxorubicin (DOX). See Preparation VI. The product is prepared by complexing DOX with CD then adding BDE to crosslink the CDs and entrap the DOX. However, given the available hydroxy and amino functional groups on the more hydrophilic area DOX, it appears more likely than not that at least some of the DOX would end up crosslinked and tethered to the polymeric product. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 3-5, 7, 10-16, 19, 20, 27 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by either of (1) Hristova-Kazmierski et al (Bioorg. Med. Chem. Lett., 1993)—also claim 6; (2) Minami et al (J. Pharm. Sci., 1998)—also claims 8 and 9; (3) Yano et al (J. Pharm. Sci., 2001)—also claims 8 and 9; or (4) Tanaka et al (US 5,183,883)—also claims 8 and 9.

The minimum requirements for claims 3 and 4 are (1) a CD and (2) a therapeutic agent wherein these two components are covalently attached. Cyclodextrins having a conjugated drug are known in the art. The art cited are representative examples.

(1) Hristova-Kazmierski discloses a δ opioid agonist to cyclodextrin. See entire reference. (2) Minami discloses biphenyl acetic acid conjugated to a cyclodextrin. See entire reference. (3) Yano discloses prednisolone conjugated to a cyclodextrin. See entire reference. (4) Tanaka discloses a conjugate of doxorubicin and cyclodextrin. See entire reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20, 27 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosak (US 6,048,736).

Kosak teaches as set forth above. The reference does not exemplify the full scope of active agents and/or ligands. Neither does the reference exemplify a polymer having both a ligand and a therapeutic agent. However, the reference specifically teaches an embodiment of the CD polymers comprising a covalently tethered guest and a covalently coupled biorecognition molecule (targeting ligand). See col 7, beginning line 65, continuing through col 8, line 57. The preferred guests are therapeutic agents described at col 3-4. Targeting ligands are described at col 4-6. The reference does not specifically teach the preparation of polymers having therapeutic

agents covalently attached via biohydrolyzable bonds. However, the reference expressly suggests the use of particular reagents for coupling and crosslinking. See col 10-11. The use of many of these would result in the type of bonds recited in the instant claims. Furthermore, the reference teaches that the guest is released upon cleavage of particular bonds in the polymer structure and specifically suggests biocleavable crosslinks. See col 8, lines 42-46 and col 9, lines 10-34.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the cyclodextrin polymers of Kosak having both a therapeutic agent and a ligand for targeted delivery of said therapeutic agent. The artisan would reasonably expect success in preparing and administering such a polymer because is it expressly suggested by the reference. It would be further obvious to prepare such products having biohydrolyzable bonding between the polymer and therapeutic agent. Kosak had taught similar reagents for both crosslinking the polymers and coupling ligand and therapeutic agents to them and that biodregadation of the crosslinked polymer is necessary to release an "entrapped" guest. Similarly, it would be obvious to one of ordinary skill that a biohydrolyzable bond between the active agent and the polymer would facilitate the release of said agent *in vivo*. In the absence of unexpected results, it would be within the scope of the artisan to optimize the molecular weight of the products through routine experimentation. It would be further obvious to prepare pharmaceutical compositions of these products for their art-disclosed utility as drug carriers.

Claims 1- 5, 7, 10-20, 27, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (WO 00/01734).

Gonzalez teaches as set forth above. As discussed above, regarding claim 34, it appears that the reference discloses a polymer comprising a plurality of folic acid moieties. However, it is possible that the compound has only a single folic acid. However, the reference expressly suggests the use of a plurality of ligands, which may be the same or different, and some of the suggested ligands are also embraced by the definition of therapeutic agent.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a Gonzalez polymer having a plurality of ligands, such as the specifically suggested folic acid or folic acid and the specifically suggested transferrin, because such a product is expressly suggested by the reference. A product having non-identical ligands would also be considered a product having both a ligand and a therapeutic agent because both of these agents have both activities.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 10-15, 20, 27 and 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) claim 7 of U.S. Patent No. 6,884,789 or (2) claim 4 of U.S. Patent No. 6,509,323. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to CD-polymers requiring the covalent attachment of a therapeutic agent. The CD-polymers recited in the cited patents require the covalent attachment of a targeting ligand. As discussed above, these categories are overlapping. For example, in each of the cited patents, it would be obvious to one of ordinary skill to prepare the preferred embodiments disclosed in each of the specifications. These are CD-polymers having folic acid or transferrin. See examples in both patents. As discussed above, each of these also has therapeutic activity. Therefore, the instant claims would be rendered obvious.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more. Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished application is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

Leigh C. Maier

Leigh C. Maier
Primary Examiner
April 28, 2006